

1 **METHOD FOR SYNTHESIZING CHIRAL BICYCLIC**
2 **THIAZOLIDINE HYDANTOIN**

3 **BACKGROUND OF THE INVENTION**

4 **1. Field of the Invention**

5 The present invention relates to a method for synthesizing chiral
6 bicyclic thiazolidine hydantoin, and more particularly to a method that
7 synthesizes chiral bicyclic thiazolidine hydantoin having high purity but by
8 using only one reacting chamber.

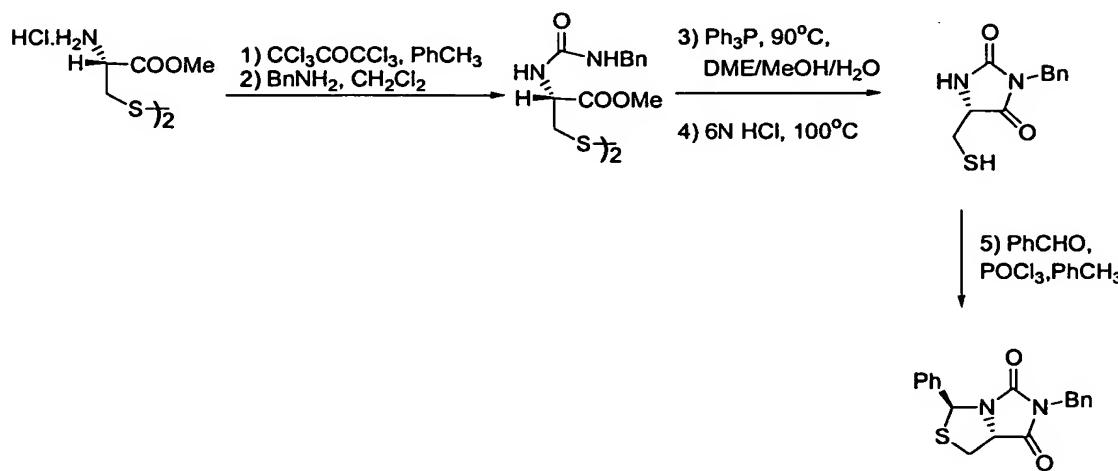
9 **2. Description of Related Art**

10 Biochips are used to obtain biotic information and each biochip
11 basically composes a substrate made of glass or a Nylon membrane and
12 multiple probes made of single-strand DNA, protein, antigen, or antibody
13 attached to the substrate. The probes hybridize with target sequences and are
14 processed to generate signals such as luminescent spots. Then, the signals are
15 analyzed, compared with a built-in database, judged, and translated to
16 become useful bio-information. The biochips are classified into three types
17 by different characteristics, which are gene-chips (i.e. DNA microarray), lab-
18 on-a-chips, and protein-chips. Wherein, the gene-chip has several advantages
19 of rapid screening, precise detection and mass sample sieving. Thus, in the
20 post-gene age, the biochips improve the progress of automatic gene analysis
21 and are the most prominent products in biotech industry.

22 Bioactive bicyclic thiazolidine hydantoin is a key intermediate to
23 synthesize biotin that is a labeling material applied on a protein or a DNA
24 sequence. Prior patents US4009172, US4130713, US4337345, US4550075,

1 US4732987, US4837402, US4877882, US4937351, US5250699, US506834,
2 US5095118 and EP0243734 disclosed several methods for preparing biotin
3 by bicyclic thiazolidine hydantoin, but rarely mentioned methods for
4 synthesizing bicyclic thiazolidine hydantoin.

5 According to records of Chem. Ber. 1948, Vol. 81, p210 and
6 Tetrahedron Lett. 1988, Vol. 29, p57, a method for synthesizing bicyclic
7 thiazolidine hydantoin is to use L-cystine dimethyl ester dihydrochloride as a
8 reactant to react with proper chemical agents. The synthesizing reaction in
9 the method is shown as follows:



10

11

12 However, the foregoing method in the records has the following
13 drawbacks:

- 14 1. The synthesizing reaction takes an excessive amount of time since
15 there are 5 steps in the reaction.
- 16 2. The chemical agents are expansive and have toxicity.
- 17 3. Other waste products such as triphenylphosphine oxide, are
18 difficult to treat, even in a furnace.

- 1 4. It is difficult to crystallize bicyclic thiazolidine hydantoin.
2 5. The purifying process of bicyclic thiazolidine hydantoin is
3 complex.

4 Based on those drawbacks, the foregoing method is not suitable for
5 industrial manufacturing.

6 Another method for synthesizing bicyclic thiazolidine hydantoin is
7 disclosed in records of Chimia 1987, Vol. 41, p148 and the Journal of
8 Organic Chemistry 1955, Vol. 60, p320-321, wherein L-(+)-Cysteine is
9 reacted with benzyl aldehyde to generate 4(R)-carboxy-2-phenylthiazolidine
10 in a first cycloaddition reaction. Then, the generated 4(R)-carboxy-2-
11 phenylthiazolidine is purified and further mixed with benzylisocyanate to
12 compose bicyclic thiazolidine hydantoin in a second cycloaddition reaction.
13 However, this method still has the following drawbacks:

- 14 1. Cycloaddition reactions and purifying processes in this method
15 have to be separately carried out which causes a low product rate
16 and unstable quality of bicyclic thiazolidine hydantoin.
17 2. It is difficult to crystallize bicyclic thiazolidine hydantoin.
18 3. This method requires an excessive amount of time to carry out the
19 separately multiple cycloaddition reactions and purifying
20 processes.

21 Therefore, this method is also not suitable for industrial
22 manufacturing.

23 The present invention has arisen to provide a method for
24 synthesizing bicyclic thiazolidine hydantoin to overcome and obviate the

1 drawbacks of the conventional methods.

2 **SUMMARY OF THE INVENTION**

3 A first objective of the present invention is to provide a method for
4 synthesizing bicyclic thiazolidine hydantoin, which carries out
5 cycloadditions twice in only one reacting chamber (one-pot) to conveniently
6 generate bicyclic thiazolidine hydantoin.

7 A second objective of the present invention is to provide a method
8 for synthesizing bicyclic thiazolidine hydantoin, which does not need to
9 isolate intermediate during operating so that the method is simplified to save
10 manufacturing costs, and eased from treating waste generated in an isolating
11 process.

12 A third objective of the present invention is to provide a method for
13 synthesizing bicyclic thiazolidine hydantoin, which shortens reaction time
14 and simplifies a purifying process to avoid washing bicyclic thiazolidine
15 hydantoin away.

16 A fourth objective of the present invention is to provide a method for
17 synthesizing bicyclic thiazolidine hydantoin, which adds molecular sieves to
18 remove water from the cycloaddition reactions to increase the crystallization
19 degree of bicyclic thiazolidine hydantoin, wherein the molecular sieves can
20 be recycled.

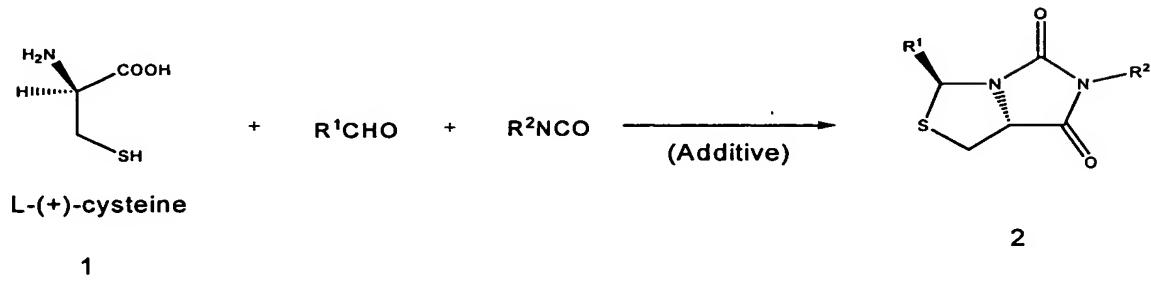
21 Further benefits and advantages of the present invention will become
22 apparent after a careful reading of the detailed description in company with
23 the drawings.

24 **BRIEF DESCRIPTION OF THE DRAWINGS**

1 Figs. 1A-1B are schematic flowcharts of a method for synthesizing
2 bicyclic thiazolidine hydantoin in accordance with the present invention,
3 wherein the method is carried out within only one reacting chamber.

4 DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

5 A method for synthesizing chiral bicyclic thiazolidine hydantoin in
6 accordance with the present invention comprises the following chemical
7 equation:



9 wherein R¹ and R² are selected from the group comprising a
10 hydrogen, phenyl, benzyl, alkyl group containing 1-5 carbon atoms, aryl
11 alkyl group in which the alkyl containing 1-5 carbon atoms.

Wherein R¹ is preferred to be phenyl and R² is preferred to be benzyl.

13 The chemical equation in the present invention basically has two
14 main reactions:

(1) L-(+)-Cysteine (compound 1) and an aldehyde are reactants and dissolved in an organic alcohol solvent to carry out a first cycloaddition to generate white intermediate, 4(R)-carboxy-2-phenylthiazolidine.

(2) Solid molecular sieves and preferred benzylisocyanate are added into 4(R)-carboxy-2-phenylthiazolidine to carry out a second cycloaddition to generate bicyclic thiazolidine hydantoin. Lastly,

1 an alcohol solvent is added into the reaction to accelerate
2 crystallization of bicyclic thiazolidine hydantoin (compound 2).
3 In the second cycloaddition, a ketone solvent and an ester solvent
4 are respectively used to dissolve the reactants.

5 With reference to Figs. 1A and 1B, a detailed description of the
6 method for synthesizing bicyclic thiazolidine hydantoin is illustrated in
7 accordance with the drawings. L-(+)-Cysteine (compound 1) and an
8 aldehyde or derivatives of the aldehyde are initial reactants and inputted into
9 a reacting chamber with a bottom as shown in the drawings. An organic
10 alcohol-water solvent (water : organic alcohol=1:1) and an organic alkali are
11 conducted into the reacting chamber. The first cycloaddition occurs to last
12 for 2 hours at room temperature (25°C) to generate white solid intermediate,
13 4(R)-carboxy-2-phenylthiazolidine. The organic alcohol-water solvent is
14 trapped out by a vacuum system and then 4(R)-carboxy-2-phenylthiazolidine
15 is dried by blowing nitrogen gas. Preferred benzylisocyanate, or derivatives
16 of isocyanate are dissolved in a ketone solvent and introduced into the
17 reacting chamber to react with the intermediate in the second cycloaddition,
18 wherein the ketone contains 2 to 5 carbon atoms. The second cycloaddition
19 occurs to last for 2 hours at 25 to 30 °C. Then, the ketone solvent is extracted
20 out by the vacuum system. An ester solvent or an ether solvent and an
21 inorganic acid are added into the reacting chamber to achieve a mixed
22 solution, wherein alkyl of the ester or the ether contains 1 to 4 carbon atoms.
23 Then, solid molecular sieves are inputted into the mixed solution. The mixed
24 solution is stirred for 2 hours at 25 °C to 30 °C. After stirring, the mixed

1 solution is steady placed to make the mixed solution separate into two layers,
2 one is an upper ester layer or an upper ether at the top and the other is an
3 aqueous layer with the solid molecular sieves at the bottom. The aqueous
4 layer and the solid molecular sieves are drained out of the reacting chamber
5 via an outlet at the bottom of the reacting chamber. The ester solvent or ether
6 solvent is extracted out by the vacuum system. Then, an alcohol solvent
7 containing 1 to 4 carbon atoms is added into the reacting chamber to enforce
8 crystallization of bicyclic thiazolidine hydantoin within 10 minutes. Again,
9 the vacuum system is operated to remove the residual alcohol solvent. Lastly,
10 crystallization of bicyclic thiazolidine hydantoin is dried in a vacuum drying
11 apparatus to obtain final white solid bicyclic thiazolidine hydantoin
12 (compound 2). Thereby, the first and second cycloadditions are realized in a
13 singular reacting chamber to synthesize bicyclic thiazolidine hydantoin.

14 The organic alkali is sodium acetate or potassium acetate. The solid
15 molecular sieves are in the form of particles having 3Å –to 5Å bore
16 diameters. The ether having 1 to 4 carbons is preferred to be diethyl ether.
17 The ester having 1 to 4 carbons is selected from the group comprising methyl
18 formate, ethyl formate, methyl acetate, ethyl acetate, and propyl acetate. The
19 inorganic acid is 6N hydrochloric acid.

20 The reacting chamber shown in Figs. 1A and 1B is designed to carry
21 out synthesis, and filtering processes without isolating intermediate in this
22 method. Additionally, the solvents are extracted out by the vacuum system
23 after the first cycloaddition reaction to allow directly operating the second
24 cycloaddition reaction without changing the reacting chamber. Therefore,

1 operational procedures of the present invention are simplified so that
2 synthesizing efficiency is increased and product loss is decreased.

3 Moreover, the solid molecular sieves are added into the reaction to
4 remove water and to increase the crystallizing rate of bicyclic thiazolidine
5 hydantoin. The solid molecular sieves are enabled to be recycled and reused
6 to decrease waste in this method.

7 The following examples are shown to further illustrate details in the
8 present invention.

9 <Example 1>

10 Initially, 1000g of L-(+)-Cysteine (8.3 moles), 880g of benzyl
11 aldehyde (8.3 moles), 750g of sodium acetate (9.1 moles) were introduced
12 into a 10L reacting chamber. Then, 4L of water and 4L of methanol were
13 poured into the reacting chamber to dissolve the chemicals to become a
14 solution. The solution was stirred for 2 hours at 25°C and then a white solid
15 appeared in the solution. The white solid was examined and determined as of
16 4(R)-carboxy-2-phenylthiazolidine (see the Appendix 1, NMR hydrogen
17 spectrum). Nitrogen gas was introduced to flow through the reacting
18 chamber and lasted for 30 minutes to remove residual methanol. Then, 500g
19 of 3Å molecular sieves and 1320g of benzylisocyanate (9.9 moles) were
20 added into the solution. Next, 5L of acetone was conducted into the solution.
21 The solution was stirred for 2 hours at 25 °C. After stirring, the acetone was
22 extracted out of the solution by a vacuum extracting device. Then, 3L of
23 ethyl acetate and 3L of 6N hydrochloric acid were added into the solution.
24 Again, the solution was stirred for 2 hours at 25°C and stably placed for 10

1 minutes until the solution was separated into an upper ethyl acetate layer and
2 a lower aqueous layer with deposited molecular sieves. The lower aqueous
3 layer and the deposited molecular sieves were drained out of the reacting
4 chamber. The ethyl acetate layer remaining in the reacting chamber was
5 extracted by the vacuum extracting device to remove the ethyl acetate.
6 Within 10 minutes, 4L of methanol was introduced into the reacting chamber
7 to enforce crystallization of bicyclic thiazolidine hydantoin in the form of a
8 white solid. Residual methanol was extracted from the white solid by
9 nitrogen gas flowing through the reacting chamber. Lastly, the bicyclic
10 thiazolidine hydantoin was dried in a vacuum drying apparatus at 20⁰C for 3
11 hours to obtain a final product, 2522g of bicyclic thiazolidine hydantoin
12 (86% producing rate), having a melting point at 79 to 80⁰C. [a]_D²⁰=
13 279.83 , C=1(CH₂Cl₂).

14

15 <Example 2>

16 Initially, 1000g of L-(+)-Cysteine (8.3 moles), 880g of benzyl
17 aldehyde (8.3 moles), 750g of sodium acetate (9.1 moles) were introduced
18 into a 10L reacting chamber. Then, 4L of water and 4L of methanol were
19 poured into the reacting chamber to dissolve the chemicals to become a
20 solution. The solution was stirred for 2 hours at 25⁰C and then a white solid
21 appeared in the solution. The white solid was examined and determined as of
22 4(R)-carboxy-2-phenylthiazolidine. Nitrogen gas was introduced to flow
23 through the reacting chamber and lasted for 30 minutes to remove residual
24 methanol. Then, 500g of 4Å molecular sieves and 1320g of benzylisocyanate

1 (9.9 moles) were added into the solution. Next, 5L of acetone was conducted
2 into the solution. The solution was stirred for 2 hours at 25 °C. After stirring,
3 the acetone was extracted out of the solution by a vacuum extracting device.
4 Then, 3L of ethyl acetate and 3L of 6N hydrochloric acid were added into
5 the solution. Again, the solution was stirred for 2 hours at 25°C and stably
6 placed for 10 minutes until the solution was separated into an upper ethyl
7 acetate layer and a lower aqueous layer with deposited 4Å molecular sieves.
8 The lower aqueous layer and the deposited 4Å molecular sieves were drained
9 out of the reacting chamber. The ethyl acetate layer remaining in the reacting
10 chamber was extracted by the vacuum extracting device to remove the ethyl
11 acetate. Within 10 minutes, 4L of methanol was introduced into the reacting
12 chamber to enforce crystallization of bicyclic thiazolidine hydantoin in the
13 form of a white solid. Residual methanol was extracted from the white solid
14 by nitrogen gas flowing through the reacting chamber. Lastly, the bicyclic
15 thiazolidine hydantoin was dried in a vacuum drying apparatus at 20°C for 3
16 hours to obtain a final product, 2347g of bicyclic thiazolidine hydantoin
17 (80% producing rate), having a melting point at 80°C. $[\alpha]_D^{20} = -288.44$,
18 C=1(CH₂Cl₂).

19

20 <Example 3>

21 Initially, 1000g of L-(+)-Cysteine (8.3 moles), 880g of benzyl
22 aldehyde (8.3 moles), 750g of sodium acetate (9.1 moles) were introduced
23 into a 10L reacting chamber. Then, 4L of water and 4L of methanol were
24 poured into the reacting chamber to dissolve the chemicals to become a

1 solution. The solution was stirred for 2 hours at 25⁰C and then a white solid
2 appeared in the solution. The white solid was examined and determined as of
3 4(R)-carboxy-2-phenylthiazolidine. Nitrogen gas was introduced to flow
4 through the reacting chamber and lasted for 30 minutes to remove residual
5 methanol. Then, 500g of 5Å molecular sieves and 1320g of benzylisocyanate
6 (9.9 moles) were added into the solution. Next, 5L of acetone was conducted
7 into the solution. The solution was stirred for 2 hours at 25⁰C. After stirring,
8 the acetone was extracted out of the solution by a vacuum extracting device.
9 Then, 3L of ethyl acetate and 3L of 6N hydrochloric acid were added into
10 the solution. Again, the solution was stirred for 2 hours at 25⁰C and stably
11 placed for 10 minutes until the solution was separated into an upper ethyl
12 acetate layer and a lower aqueous layer with deposited 5Å molecular sieves.
13 The lower aqueous layer and the deposited 5Å molecular sieves were drained
14 out of the reacting chamber. The ethyl acetate layer remaining in the reacting
15 chamber was extracted by the vacuum extracting device to remove the ethyl
16 acetate. Within 10 minutes, 4L of methanol was introduced into the reacting
17 chamber to enforce crystallization of bicyclic thiazolidine hydantoin in the
18 form of a white solid. Residual methanol was extracted from the white solid
19 by nitrogen gas flowing through the reacting chamber. Lastly, the bicyclic
20 thiazolidine hydantoin was dried in a vacuum drying apparatus at 20⁰C for 3
21 hours to obtain a final product, 2200g of bicyclic thiazolidine hydantoin
22 (75% producing rate), having a melting point at 79 to 80⁰C. [a]_D²⁰=
23 280.36 , C=1(CH₂Cl₂).
24

1 <Example 4>

2 Initially, 1000g of L-(+)-Cysteine (8.3 moles), 880g of benzyl
3 aldehyde (8.3 moles), 750g of sodium acetate (9.1 moles) were introduced
4 into a 10L reacting chamber. Then, 4L of water and 4L of ethanol were
5 poured into the reacting chamber to dissolve the chemicals to become a
6 solution. The solution was stirred for 2 hours at 25⁰C and then a white solid
7 appeared in the solution. The white solid was examined and determined as of
8 4(R)-carboxy-2-phenylthiazolidine. Nitrogen gas was introduced to flow
9 through the reacting chamber and lasted for 30 minutes to remove residual
10 ethanol. Then, 500g of 3Å molecular sieves and 1320g of benzylisocyanate
11 (9.9 moles) were added into the solution. Next, 5L of acetone was conducted
12 into the solution. The solution was stirred for 2 hours at 25⁰C. After stirring,
13 the acetone was extracted out of the solution by a vacuum extracting device.
14 Then, 3L of ethyl acetate and 3L of 6N hydrochloric acid were added into
15 the solution. Again, the solution was stirred for 2 hours at 25⁰C and stably
16 placed for 10 minutes until the solution was separated into an upper ethyl
17 acetate layer and a lower aqueous layer with deposited 3Å molecular sieves.
18 The lower aqueous layer and the deposited 3Å molecular sieves were drained
19 out of the reacting chamber. The ethyl acetate layer remaining in the reacting
20 chamber was extracted by the vacuum extracting device to remove the ethyl
21 acetate. Within 10 minutes, 4L of methanol was introduced into the reacting
22 chamber to enforce crystallization of bicyclic thiazolidine hydantoin in the
23 form of a white solid. Residual methanol was extracted from the white solid
24 by nitrogen gas flowing through the reacting chamber. Lastly, the bicyclic

1 thiazolidine hydantoin was dried in a vacuum drying apparatus at 20⁰C for 3
2 hours to obtain a final product, 2405g of bicyclic thiazolidine hydantoin
3 (82% producing rate), having a melting point at 80⁰C. [a]_D²⁰=-280.59 ,
4 C=1(CH₂Cl₂).

5

6 <Example 5>

7 Initially, 1000g of L-(+)-Cysteine (8.3 moles), 880g of benzyl
8 aldehyde (8.3 moles), 750g of sodium acetate (9.1 moles) were introduced
9 into a 10L reacting chamber. Then, 4L of water and 4L of methanol were
10 poured into the reacting chamber to dissolve the chemicals to become a
11 solution. The solution was stirred for 2 hours at 25⁰C and then a white solid
12 appeared in the solution. The white solid was examined and determined as of
13 4(R)-carboxy-2-phenylthiazolidine. Nitrogen gas was introduced to flow
14 through the reacting chamber and lasted for 30 minutes to remove residual
15 methanol. Then, 500g of 3Å molecular sieves and 1320g of benzylisocyanate
16 (9.9 moles) were added into the solution. Next, 5L of acetone was conducted
17 into the solution. The solution was stirred for 2 hours at 25⁰C. After stirring,
18 the acetone was extracted out of the solution by a vacuum extracting device.
19 Then, 3L of diethyl ether and 3L of 6N hydrochloric acid were added into
20 the solution. Again, the solution was stirred for 2 hours at 25⁰C and stably
21 placed for 10 minutes until the solution was separated into an upper diethyl
22 ether layer and a lower aqueous layer with deposited 3Å molecular sieves.
23 The lower aqueous layer and the deposited 3Å molecular sieves were drained
24 out of the reacting chamber. The diethyl ether layer remaining in the reacting

1 chamber was extracted by the vacuum extracting device to remove the
2 diethyl ether. Within 10 minutes, 4L of ethanol was introduced into the
3 reacting chamber to enforce crystallization of bicyclic thiazolidine hydantoin
4 in the form of a white solid. Residual ethanol was extracted from the white
5 solid by nitrogen gas flowing through the reacting chamber. Lastly, the
6 bicyclic thiazolidine hydantoin was dried in a vacuum drying apparatus at
7 20°C for 3 hours to obtain a final product, 1995g of bicyclic thiazolidine
8 hydantoin (68% producing rate), having a melting point at 80°C. [a]_D²⁰=
9 280.36 , C=1(CH₂Cl₂).

10 <Example 6>

11 Initially, 1000g of L-(+)-Cysteine (8.3 moles), 880g of benzyl
12 aldehyde (8.3 moles), 750g of sodium acetate (9.1 moles) were introduced
13 into a 10L reacting chamber. Then, 4L of water and 4L of ethanol were
14 poured into the reacting chamber to dissolve the chemicals to become a
15 solution. The solution was stirred for 2 hours at 25°C and then a white solid
16 appeared in the solution. The white solid was examined and determined as of
17 4(R)-carboxy-2-phenylthiazolidine. Nitrogen gas was introduced to flow
18 through the reacting chamber and lasted for 30 minutes to remove residual
19 ethanol. Then, 500g of 3Å molecular sieves and 1320g of benzylisocyanate
20 (9.9 moles) were added into the solution. Next, 5L of acetone was conducted
21 into the solution. The solution was stirred for 2 hours at 25 °C. After stirring,
22 the acetone was extracted out of the solution by a vacuum extracting device.
23 Then, 3L of ethyl acetate and 3L of 6N hydrochloric acid were added into
24 the solution. Again, the solution was stirred for 2 hours at 25°C and stably

1 placed for 10 minutes until the solution was separated into an upper ethyl
2 acetate layer and a lower aqueous layer with deposited 3Å molecular sieves.
3 The lower aqueous layer and the deposited 3Å molecular sieves were drained
4 out of the reacting chamber. The ethyl acetate layer remaining in the reacting
5 chamber was extracted by the vacuum extracting device to remove the ethyl
6 acetate. Within 10 minutes, 4L of isopropanol was introduced into the
7 reacting chamber to enforce crystallization of bicyclic thiazolidine hydantoin
8 in the form of a white solid. Residual isopropanol was extracted from the
9 white solid by nitrogen gas flowing through the reacting chamber. Lastly, the
10 bicyclic thiazolidine hydantoin was dried in a vacuum drying apparatus at
11 20°C for 3 hours to obtain a final product, 2552g of bicyclic thiazolidine
12 hydantoin (87% producing rate), having a melting point at 79 to 80°C. [a]
13 $D^{20} = 280.3 \cdot C = 1(CH_2Cl_2)$.

14

15 <Example 7>

16 Initially, 1000g of L-(+)-Cysteine (8.3 moles), 880g of benzyl
17 aldehyde (8.3 moles), 750g of sodium acetate (9.1 moles) were introduced
18 into a 10L reacting chamber. Then, 4L of water and 4L of isopropanol were
19 poured into the reacting chamber to dissolve the chemicals to become a
20 solution. The solution was stirred for 2 hours at 25°C and then a white solid
21 appeared in the solution. The white solid was examined and determined as of
22 4(R)-carboxy-2-phenylthiazolidine. Nitrogen gas was introduced to flow
23 through the reacting chamber and lasted for 30 minutes to remove residual
24 isopropanol. Then, 500g of 3Å molecular sieves and 1320g of

1 benzylisocyanate (9.9 moles) were added into the solution. Next, 5L of
2 acetone was conducted into the solution. The solution was stirred for 2 hours
3 at 25 °C. After stirring, the acetone was extracted out of the solution by a
4 vacuum extracting device. Then, 3L of ethyl acetate and 3L of 6N
5 hydrochloric acid were added into the solution. Again, the solution was
6 stirred for 2 hours at 25°C and stably placed for 10 minutes until the solution
7 was separated into an upper ethyl acetate layer and a lower aqueous layer
8 with deposited 3Å molecular sieves. The lower aqueous layer and the
9 deposited 3Å molecular sieves were drained out of the reacting chamber. The
10 ethyl acetate layer remaining in the reacting chamber was extracted by the
11 vacuum extracting device to remove the ethyl acetate. Within 10 minutes, 4L
12 of methanol was introduced into the reacting chamber to enforce
13 crystallization of bicyclic thiazolidine hydantoin in the form of a white solid.
14 Residual methanol was extracted from the white solid by nitrogen gas
15 flowing through the reacting chamber. Lastly, the bicyclic thiazolidine
16 hydantoin was dried in a vacuum drying apparatus at 20°C for 3 hours to
17 obtain a final product, 2347g of bicyclic thiazolidine hydantoin (80%
18 producing rate), having a melting point at 80°C. [a]_D²⁰=-280.01 ,
19 C=1(CH₂Cl₂).
20

21 <Example 8>

22 Initially, 1000g of L-(+)-Cysteine (8.3 moles), 880g of benzyl
23 aldehyde (8.3 moles), 750g of sodium acetate (9.1 moles) were introduced
24 into a 10L reacting chamber. Then, 4L of water and 4L of isopropanol were

1 poured into the reacting chamber to dissolve the chemicals to become a
2 solution. The solution was stirred for 2 hours at 25°C and then a white solid
3 appeared in the solution. The white solid was examined and determined as of
4 4(R)-carboxy-2-phenylthiazolidine. Nitrogen gas was introduced to flow
5 through the reacting chamber and lasted for 30 minutes to remove residual
6 isopropanol. Then, 500g of 3Å molecular sieves and 1320g of
7 benzylisocyanate (9.9 moles) were added into the solution. Next, 5L of
8 acetone was conducted into the solution. The solution was stirred for 2 hours
9 at 25 °C. After stirring, the acetone was extracted out of the solution by a
10 vacuum extracting device. Then, 3L of ethyl acetate and 3L of 6N
11 hydrochloric acid were added into the solution. Again, the solution was
12 stirred for 2 hours at 25°C and stably placed for 10 minutes until the solution
13 was separated into an upper ethyl acetate layer and a lower aqueous layer
14 with deposited 3Å molecular sieves. The lower aqueous layer and the
15 deposited 3 Å molecular sieves were drained out of the reacting chamber.
16 The ethyl acetate layer remaining in the reacting chamber was extracted by
17 the vacuum extracting device to remove the ethyl acetate. Within 10 minutes,
18 4L of ethanol was introduced into the reacting chamber to enforce
19 crystallization of bicyclic thiazolidine hydantoin in the form of a white solid.
20 Residual ethanol was extracted from the white solid by nitrogen gas flowing
21 through the reacting chamber. Lastly, the bicyclic thiazolidine hydantoin was
22 dried in a vacuum drying apparatus at 20°C for 3 hours to obtain a final
23 product, 2376g of bicyclic thiazolidine hydantoin (81% producing rate),
24 having a melting point at 79 to 80°C. [a] _D²⁰=-280.59 , C=1(CH₂Cl₂).

1

2 <Example 9>

3 Initially, 1000g of L-(+)-Cysteine (8.3 moles), 880g of benzyl
4 aldehyde (8.3 moles), 750g of sodium acetate (9.1 moles) were introduced
5 into a 10L reacting chamber. Then, 4L of water and 4L of isopropanol were
6 poured into the reacting chamber to dissolve the chemicals to become a
7 solution. The solution was stirred for 2 hours at 25⁰C and then a white solid
8 appeared in the solution. The white solid was examined and determined as of
9 4(R)-carboxy-2-phenylthiazolidine. Nitrogen gas was introduced to flow
10 through the reacting chamber and lasted for 30 minutes to remove residual
11 isopropanol. Then, 500g of 3Å molecular sieves and 1320g of
12 benzylisocyanate (9.9 moles) were added into the solution. Next, 5L of
13 acetone was conducted into the solution. The solution was stirred for 2 hours
14 at 25⁰C. After stirring, the acetone was extracted out of the solution by a
15 vacuum extracting device. Then, 3L of ethyl acetate and 3L of 6N
16 hydrochloric acid were added into the solution. Again, the solution was
17 stirred for 2 hours at 25⁰C and stably placed for 10 minutes until the solution
18 was separated into an upper ethyl acetate layer and a lower aqueous layer
19 with deposited 3Å molecular sieves. The lower aqueous layer and the
20 deposited 3 Å molecular sieves were drained out of the reacting chamber.
21 The ethyl acetate layer remaining in the reacting chamber was extracted by
22 the vacuum extracting device to remove the ethyl acetate. Within 10 minutes,
23 4L of methanol was introduced into the reacting chamber to enforce
24 crystallization of bicyclic thiazolidine hydantoin in the form of a white solid.

1 Residual methanol was extracted from the white solid by nitrogen gas
2 flowing through the reacting chamber. Lastly, the bicyclic thiazolidine
3 hydantoin was dried in a vacuum drying apparatus at 20⁰C for 3 hours to
4 obtain a final product, 2464g of bicyclic thiazolidine hydantoin (84%
5 producing rate), having a melting point at 80⁰C. [a]_D²⁰=-280.10 ,
6 C=1(CH₂Cl₂).

7

8 <Example 10>

9 Initially, 1000g of L-(+)-Cysteine (8.3 moles), 880g of benzyl
10 aldehyde (8.3 moles), 750g of sodium acetate (9.1 moles) were introduced
11 into a 10L reacting chamber. Then, 4L of water and 4L of methanol were
12 poured into the reacting chamber to dissolve the chemicals to become a
13 solution. The solution was stirred for 2 hours at 25⁰C and then a white solid
14 appeared in the solution. The white solid was examined and determined as of
15 4(R)-carboxy-2-phenylthiazolidine. Nitrogen gas was introduced to flow
16 through the reacting chamber and lasted for 30 minutes to remove residual
17 methanol. Then, 500g of 3Å molecular sieves and 1320g of benzylisocyanate
18 (9.9 moles) were added into the solution. Next, 5L of acetone was conducted
19 into the solution. The solution was stirred for 2 hours at 25⁰C. After stirring,
20 the acetone was extracted out of the solution by a vacuum extracting device.
21 Then, 3L of ethyl acetate and 3L of 6N hydrochloric acid were added into
22 the solution. Again, the solution was stirred for 2 hours at 25⁰C and stably
23 placed for 10 minutes until the solution was separated into an upper ethyl
24 acetate layer and a lower aqueous layer with deposited 3Å molecular sieves.

1 The lower aqueous layer and the deposited 3 Å molecular sieves were
2 drained out of the reacting chamber. The ethyl acetate layer remaining in the
3 reacting chamber was extracted by the vacuum extracting device to remove
4 the ethyl acetate. Within 10 minutes, 4L of isopropanol was introduced into
5 the reacting chamber to enforce crystallization of bicyclic thiazolidine
6 hydantoin in the form of a white solid. Residual isopropanol was extracted
7 from the white solid by nitrogen gas flowing through the reacting chamber.
8 Lastly, the bicyclic thiazolidine hydantoin was dried in a vacuum drying
9 apparatus at 20°C for 3 hours to obtain a final product, 2493g of bicyclic
10 thiazolidine hydantoin (85% producing rate), having a melting point at 78 to
11 79°C. [a]_D²⁰=-279.59, C=1(CH₂Cl₂).

12 According to the foregoing examples, each example obtains a high-
13 purity white solid of bicyclic thiazolidine hydantoin that is tested for analysis
14 by NMR and HPLC and shown in the Appendixes 3 to 5. Appendixes 1 and
15 2 are spectrums respectively representing ¹H standard test and ¹³C standard
16 test to clarify the intermediate 4(R)-carboxy-2-phenylthiazolidine.
17 Appendixes 3 and 4 are spectrums respectively representing ¹H standard test
18 and ¹³C standard test to clarify the final product, bicyclic thiazolidine
19 hydantoin. Appendix 5 is an HPLC testing result to show the purity of
20 obtained bicyclic thiazolidine hydantoin. The standard sample shown in
21 Appendix 5 was tested under the following operational conditions:

22 HPLC Type

23 Pump :Waters 600E

24 Detector :Waters 2996 Photodiode Array Detector

1 Autosampler :Waters 717 plus

2 Mobile phase :1% TEA, pH7.5 / MeOH=40 / 60

3 Flow rate :1.0 mL/min

4 Column :Inertsil 5 ODS-80A, 3.2*250-mm

5 Column Oven :40C

6 Wavelength :254nm

7 RT : peak at 1 min indicates a retention time for methanol.

8 RT : peak at 13.797 min indicates a retention time for bicyclic

9 thiazolidine hydantoin ($R^1=Ph$, $R^2=PhCH_2$).

10 RT : retention time

11

12 According to the examples and experimental data, the method for

13 synthesizing chiral bicyclic thiazolidine hydantoin can synthesize bicyclic

14 thiazolidine hydantoin by two cycloadditions within only a singular reacting

15 chamber without isolating the intermediate (so-called one-pot operation) and

16 has high producing rate over and about 80%. Therefore, operational

17 procedures are simplified in a convenient way and operational time is

18 decreased, whereby this method has excellent economic benefits.

19 Additionally, the solid molecular sieves increase the crystallization degree of

20 bicyclic thiazolidine hydantoin. Therefore, the two main drawbacks of the

21 conventional method for manufacturing bicyclic thiazolidine hydantoin are

22 eliminated in the present invention.

23 Although the invention has been explained in relation to its preferred

24 embodiment, many other possible modifications and variations can be made

1 without departing from the spirit and scope of the invention as hereinafter
2 claimed.